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CLINICAL PERSPECTIVE

Gender-affirming hormone therapy for transgender and gender-diverse adults in Australia

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Abstract

Gender-affirming hormone therapy (GAHT) is used by many transgender and gender-diverse adults to align physical characteristics with their gender identity, reduce gender incongruence and improve psychological functioning. This narrative review provides an overview of the initiation and monitoring of GAHT in an Australian context. Trans individuals treated with testosterone typically receive standard testosterone doses and formulations recommended for cisgender men, whereas those receiving estradiol GAHT are typically treated with estradiol in combination with an anti-androgen in those without orchidectomy. Proactive monitoring and mitigation of cardiovascular risk factors is pertinent in all transgender and gender-diverse adults and bone health is an important consideration in those using estradiol GAHT.

Introduction

Transgender and gender-diverse (trans) people are those whose gender identity is different from their sex recorded at birth. An individual's gender identity may be binary (male or female) or non-binary (not exclusively male or female, e.g. agender, gender fluid). A non-binary gender identity can be a gender identity itself but can also be used as an umbrella term for gender identities that are not exclusively male or female. There has been an exponential increase in the number of trans people seeking medical care, and current population-based estimates suggest that 0.5–2.8% of the general population are trans.[1,2]

There are many ways in which trans people may affirm their gender without medical intervention. This can include the use of preferred name and pronouns, changes to appearance, or voice therapy. However, many trans people desire gender-affirming hormone therapy (GAHT) to align physical characteristics with their gender identity, which reduces gender incongruence and improves mental health.[3–5] Commencement of GAHT is typically a highly considered decision after balancing potential benefits on psychological functioning with potential medical and social risks.[6]

This narrative review aims to provide a practical update on the initiation and monitoring of GAHT for trans adults in Australia, as well as an approach to common scenarios that arise in clinical practice.

Models of care

Broadly, there are two models of care for the initiation of GAHT in trans adults: a formal assessment and approval by a mental health practitioner (World Professional Association of Transgender Health (WPATH) model) or the informed consent model of care. In the traditional formal assessment model, a mental health practitioner approves medical therapy following a comprehensive assessment to confirm gender dysphoria and stable mental health.[7] However, this model has been criticised for gatekeeping and inaccessibility,[8,9] and

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recommendations for assessment were subsequently extensively revised in the 2022 WPATH Standards of Care.[10]

In the informed consent model of care, the decision to commence GAHT is a shared decision-making process between the patient and the clinician. In this model, the treating clinician assesses an individual's ability to provide informed consent and provides education regarding the potential risks and benefits of GAHT, including the role of fertility preservation. This model places the patient as the primary decision-maker in partnership with the clinician. It aims to depathologise gender diversity and does not mandate a formal psychiatric assessment. The informed consent model is commonly used in Australia and is associated with high patient satisfaction.[11] Consent forms for the initiation of GAHT are available in Australian Professional Association for Trans Health (AusPATH) Informed Consent Standards of Care for GAHT.[12]

There are limited data comparing the two models of care, and both are used by practitioners experienced in trans health.[13] Australian data have shown that the informed consent model is associated with a reduced number of clinic visits and time to initiation of GAHT.[14] Individuals undergoing formal assessment have a higher number of psychiatric diagnoses,[14] with a history of schizophrenia or post-traumatic stress disorder being associated with referral for formal assessment rather than the informed consent model.[11] The formal assessment model should be considered if there are any concerns regarding an individual's capacity to provide informed consent.

Regardless of the model of care, ensuring appropriate review and education of relative contraindications is paramount to ensure the safe provision of GAHT. For example, transdermal estradiol should be preferentially offered over oral estradiol in circumstances where an individual is at higher risk of venous thromboembolic disease, such as class III obesity or smoking. Similarly, education and specialist referral should be considered in individuals with a personal or family history of hormone-sensitive malignancy.

Testosterone therapy for gender affirmation

Trans people recorded female at birth who commence testosterone GAHT will typically achieve serum testosterone concentrations in the cisgender male reference range (approximately 10–30 nmol/L).[10,15] This induces physical changes, including increased muscle mass, body fat redistribution, voice deepening and facial and body hair growth (Table 1).

Table 1 Timeline of physical changes with testosterone therapy in trans individuals

Clinical effect	Onset	Maximal changes
Skin oiliness/acne[16]	1–6 months	1–2 years
Facial/body hair growth[17]	6–12 months	4–5 years
Scalp hair loss[17]	6–12 months	-
Increased muscle mass/strength[18]	6–12 months	2–5 years
Body fat redistribution[18]	1–6 months	2–5 years
Cessation of menses[19]	1–6 months	-
Clitoral enlargement[20]	1–6 months	1–2 years
Vaginal atrophy	1–6 months	1–2 years
Deepening of voice[21,22]	6–12 months	1–2 years
Increased libido[23]	3 months	-

Adapted from Hembree *et al.*[15]

Table 2 Testosterone formulations available in Australia

Formulation	Standard dosing regimen
Intramuscular	
Testosterone undecanoate (Reandron)†	1000 mg every 10–14 weeks (loading dose at 6 weeks)
Testosterone enanthate (Primoteston)‡	250 mg every 2–4 weeks
Transdermal	
1% testosterone gel (Testogel)†	4 pump actuations (12.5 mg/actuation) daily 1 sachet (50 mg/5 g) daily
2% testosterone gel (Testavan)†	1–2 pump actuations (23-46 mg) daily
5% testosterone cream (AndroForte)§	2 mL (50 mg/mL) daily

†Available on the Australian Pharmaceutical Benefits Scheme (PBS).
‡No longer available on the PBS from 1 February 2018.
§Available on the PBS for application to the scrotal area from 1 July 2021.

Testosterone formulations

Testosterone is administered through the intramuscular or transdermal route. Standard doses and formulations recommended for cisgender hypogonadal men are recommended in consensus guidelines,[6,10,15] although some non-binary people request lower doses to promote slow or lesser degrees of masculinisation. Intramuscular testosterone undecanoate is the preferred first-line treatment option among practitioners experienced in trans health care in Australia[13] and is the most commonly prescribed formulation.[24] Testosterone formulations available in Australia and corresponding full-dose regimens are shown in Table 2. Of these, intramuscular testosterone undecanoate, 1% testosterone gel and 2% testosterone gel are available on the Australian Pharmaceutical Benefits Scheme (PBS) using the authority indication 'androgen deficiency due to an established testicular disorder'.[6]

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Monitoring

For those using transdermal testosterone gel or cream, serum total testosterone concentrations are typically checked at baseline, every 3–4 months in the first year and then annually once levels are adequate and stable.[6] For those using intramuscular testosterone undecanoate, steady state is only achieved after the fourth injection, and the first blood test for monitoring and dose adjustment should be performed just prior to the fourth injection with aim through total testosterone concentration of 10–15 nmol/L. Measurement of serum testosterone concentrations should always occur at the end of an injection interval (through testosterone concentration). Serum concentrations below the normal range (i.e. <10 nmol/L) would indicate the need for a shorter injection interval and high serum trough total testosterone concentrations (i.e. >15 nmol/L) would necessitate an extension of the injection interval. Serum testosterone concentration targets are based on cisgender male reference ranges.[6,15] However, trans, including non-binary people who desire gradual physical changes or a more androgynous appearance, may desire lower testosterone doses, with resultant target serum total testosterone concentrations potentially between the cisgender male and female reference ranges.[25]

Adverse effects

An approach to common adverse effects with testosterone treatment is detailed below.

Polycythaemia with testosterone therapy

Polycythaemia is the most common adverse effect of testosterone treatment. In trans people undergoing testosterone therapy, haemoglobin and haematocrit levels should be compared with the male reference range.[26] If the haematocrit level is >0.5, it is important to exclude other contributory factors (e.g. smoking) and consider decreasing the testosterone dose or increasing the dosing interval.[27] Transdermal testosterone is associated with a lower risk of polycythaemia, so it represents a potential option for individuals who develop polycythaemia on intramuscular formulations.[28]

Persistent menstruation with testosterone therapy

Menstrual cessation usually occurs within 1 to 6 months of testosterone therapy but can continue beyond 12 months.[19] If persistent menstruation results in significant dysphoria, potential options include increasing the testosterone dose, oral progestins (e.g. norethisterone), progestin-releasing intrauterine devices or surgery as appropriate.

Acne with testosterone therapy

Acne peaks at 6 months following testosterone therapy and gradually improves over time.[16,29] Topical retinoids or retinoid-benzoyl peroxide combinations are useful for mild to moderate acne, whereas oral antibiotics or isotretinoin may be required for moderate to severe acne.[6]

Androgenic alopecia with testosterone therapy

Androgenic alopecia is a documented adverse effect of testosterone treatment.[17] Finasteride and/or minoxidil can be trialled, although there is a lack of supportive data in the trans population.

Pelvic pain with testosterone therapy

Observational studies have documented associations between testosterone and pelvic pain, with higher odds reported in individuals with persistent menstruation, current or previous history of post-traumatic stress disorder and pain with orgasm.[30] Although the aetiology can be unclear, referral to pelvic floor physiotherapists can be considered.

Estradiol therapy for gender affirmation

Trans individuals seeking feminisation are typically treated with estradiol with or without an anti-androgen to increase the serum estradiol concentration and decrease serum testosterone concentration to the respective cisgender female reference ranges. This results in development of feminine physical characteristics, including softening of skin, a decrease in facial and body hair growth, breast development, and changes in body composition, including body fat redistribution and decreased muscle mass[15,18] (Table 3).

Estradiol and anti-androgen formulations

Estradiol is most commonly administered through the oral or transdermal route,[24] and oral estradiol valerate is the most common first-line treatment in Australia.[13] Estradiol formulations available in Australia are shown in Table 4. In the absence of supporting data, estradiol is typically commenced at low doses and gradually uptitrated every 2–3 months to the target range. Notably, consensus guidelines recommend transdermal estradiol formulations in trans individuals aged 45 years and older,[33] based on observations from the cisgender menopausal hormone therapy literature, where higher oral

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Table 3 Timeline of physical changes with estradiol therapy in trans individuals

Clinical effect	Onset	Maximal changes
Body fat redistribution[18]	3–6 months	2–3 years
Decrease in muscle mass and strength[18]	3–6 months	1–2 years
Softening of skin/decreased oiliness	3–6 months	Unknown
Decreased sexual desire[23]	1–3 months	3–6 months
Decreased spontaneous erections	1–3 months	3–6 months
Breast growth[31]	3–6 months	2–3 years
Decreased testicular volume[20]	3–6 months	2–3 years
Decreased sperm production[32]	Unknown	>3 years
Decreased growth of body and facial hair[16]	6–12 months	>3 years

Adapted from Hembree *et al.*[15]

Table 4 Estradiol formulations available in Australia

Formulation	Standard dosing regimen
Oral	
Estradiol valerate (Progynova)†	2–8 mg daily
Estradiol hemihydrate (Zumenon)†	2–8 mg daily
Transdermal	
Patch (Estradot, Estraderm)†	50–200 mcg/24 h twice weekly
Estradiol gel 0.06% (EstroGel)	2–4 pump actuations (0.75 mg/actuation) daily
Estradiol gel 0.1% (Sandrena)†	1–2 sachets (1 mg estradiol) daily

†Available on the Australian Pharmaceutical Benefits Scheme.

estradiol doses are associated with an increased risk of venous thromboembolic events.[34]

Anti-androgen therapy is often required in addition to estradiol therapy to lower endogenous testosterone or inhibit the effects of testosterone. Spironolactone (100–200 mg daily) or cyproterone acetate (12.5–25 mg daily) are commonly prescribed,[35] but there are no comparative data evaluating clinical feminisation. Both inhibit peripheral testosterone effects, but cyproterone acetate also suppresses gonadotropins and testosterone production. Case reports of prolactinoma or meningioma[36] have been reported with high-dose cyproterone acetate, and the lowest effective dose should be used.[37–39]

Progesterone

There is ongoing debate regarding the inclusion of progesterone in addition to estradiol and anti-androgen therapy.[40,41] Although there are anecdotal reports of improved sleep and breast development in trans individuals,[40] micronised progesterone is not currently recommended in consensus guidelines due to a lack of supportive evidence. Limited clinical trial data have not supported a role for micronised progesterone on breast development,[42] but higher quality research is required. Additionally, given that cyproterone acetate has progestogenic activity, it is not known if this alters biological activity or increases adverse effects if prescribed in combination. We acknowledge that micronised progesterone is used by some trans people with informed consent despite the lack of evidence in the trans population. Education should include that progesterone is responsible for lobular alveolar development to facilitate lactation but not pubertal breast development in cisgender women,[43] as well as potential adverse effects such as somnolence and depression.[6,15]

Monitoring

Consensus guidelines recommend monitoring serum estradiol and testosterone concentrations at baseline, every 3–4 months for the first year, and then annually once levels are adequate and stable.[6]

Several consensus guidelines give recommendations for target serum estradiol concentrations to allow titration of estradiol therapy.[6,15] Australian guidelines recommend targeting serum estradiol concentrations of 250–600 pmol/L (GRADE 2D recommendation) based on local cross-sectional data[6]; however, more recent AusPATH guidelines recommend 250–1000 pmol/L.[12] Maintenance of serum estradiol concentrations within this range often requires significantly higher estradiol doses than those used for menopausal hormone therapy.[24] Notably, given the lack of supportive data in trans individuals, these recommendations are based on expert opinion, and the exact value of biochemical monitoring remains unclear. In the absence of data, some clinicians prioritise testosterone suppression rather than escalation of estradiol dosing to mitigate adverse effects. There are currently no data demonstrating associations between serum estradiol concentrations and breast development,[31] body composition[44] or well-being.[45]

Adverse effects

An approach to common scenarios with estradiol treatment are detailed below.

Venous thromboembolic disease with estradiol therapy

Observational studies have shown an increased venous thromboembolism (VTE) risk in trans people using estradiol therapy.[46–48] Initial studies evaluating the safety of GAHT documented a 45-fold increased risk of VTE (occurring in 6.3%) in trans people treated with ethinyl estradiol 100 mcg daily and cyproterone acetate 100 mg daily.[49] Due to this, ethinyl estradiol and conjugated

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equine estrogens are no longer recommended.[15] Modern GAHT regimens involving oral or transdermal estradiol have a lower risk of VTE; recent observational data suggest a risk between 0% and 2%.[50–54] A systematic review and meta-analysis found the overall risk approximates that of cisgender women prescribed estradiol.[55]

Hyperprolactinaemia with estradiol therapy

Mild hyperprolactinaemia is common following initiation of estradiol-based GAHT and is mostly attributed to cyproterone acetate.[56] Although there is a paucity of data regarding routine prolactin monitoring, it is recommended if there are symptoms of hyperprolactinaemia (e.g. galactorrhoea) or pituitary tumour, such as temporal hemianopia or anterior pituitary hormone deficiency.

Perioperative estradiol

Guidelines have previously recommended withholding estradiol in the perioperative period. Recent retrospective studies have not documented an increased VTE risk with perioperative estradiol continuation in individuals undergoing genital surgery.[57,58] This should be individualised based on an individual's VTE risk, but current data do not support routine discontinuation in the perioperative period. Discontinuation of estradiol can lead to worsening dysphoria or mental health and potentially symptoms of hypogonadism such as hot flushes.

Other health considerations

Cardiovascular disease

Large-cohort and registry-based studies with population-based comparison groups have demonstrated higher rates of cardiovascular disease (CVD) in the trans population. A large-cohort study from the Netherlands reported a higher incidence of stroke and myocardial infarction in trans people undergoing estradiol therapy for gender affirmation relative to cisgender women and an elevated incidence of stroke relative to cisgender men.[59] Trans people undergoing testosterone therapy had an elevated risk of myocardial infarction compared to cisgender women but not cisgender men. Similarly, a retrospective cohort study from electronic medical records in the United States also reported higher rates of VTE and stroke in trans individuals undergoing estradiol.[52] The evidence was insufficient to draw conclusions about cardiovascular events in trans individuals undergoing testosterone GAHT.

The reasons underlying this are likely multifactorial, with high rates of cardiovascular risk factors documented in observational studies. A recent online survey from Australia documented smoking in 15% of trans individuals, higher than the population average.[60] Lipid profile is also affected by sex steroids; a systematic review and meta-analysis documented an increase in triglycerides but not low-density lipoprotein (LDL), high-density lipoprotein (HDL) or total cholesterol following ≥2 years of estradiol GAHT, whereas testosterone GAHT is associated with lower HDL and increased triglycerides and LDL.[61] Retrospective data regarding the risk of type 2 diabetes have yielded discrepant results.[62,63]

Bone health

Observational studies have demonstrated low bone mass in trans individuals before initiation of GAHT, particularly those recorded male at birth.[64] This is likely multifactorial, with vitamin D deficiency, low levels of physical activity and higher rates of smoking. Prospective studies have demonstrated improvements in areal bone mineral density after the commencement of GAHT. However, one observational study reported an association between serum estradiol concentrations in the lowest tertile (mean (range), 118 (20–182) pmol/L) and reduction in lumbar spine density.[65] On this basis, it is reasonable to ensure adequate serum vitamin D, encourage physical activity, and, for those on estradiol GAHT, ensure serum estradiol concentration >200 pmol/L. There are currently no recommendations for routine bone density screening in trans adults unless other risk factors are present. A detailed description of bone health in trans individuals undergoing GAHT has been described elsewhere.[66,67]

Cancer screening

Cancer screening should be individualised based on the presence of organs in trans people, regardless of gender identity or GAHT status. Recent data from the Netherlands has demonstrated that trans people using estradiol GAHT have breast cancer rates higher than the general male population but lower than the general female population[68] and significantly lower rates of prostate cancer compared to the general male population.[69] Trans people treated with testosterone have a lower risk of breast cancer compared to the general female population.[68]

Conclusion

GAHT is an essential treatment for many trans individuals and is associated with improvements in gender incongruence and mental health. Clinicians can initiate GAHT under the informed consent model of care, and there is an emerging body of literature supporting its use in trans adults. Proactive monitoring and mitigation of cardiovascular risk factors is pertinent in all trans people,

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and bone health is an important consideration in those undergoing estradiol therapy for gender affirmation.

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